Molecular Drive

While, in general, we have few quibbles with the substance of Roger Lewin's clear description of the genetic system of molecular drive (Research News, 5 Nov., p. 552), several comments in his article merit further discussion.

In our two papers (*1*) in which we detailed the factual basis and theoretical implications of molecular drive, we defined it as a process of fixing a mutation within multigene and nongenic families in a population, as a consequence of DNA turnover. Considerations of rates of turnover indicate that individuals of a sexual population would change in unison with respect to the changing composition of a family. At the heart of molecular drive is the widespread phenomenon of concerted evolution. Although the reality of this phenomenon is incontestable, we cannot accept the definitive statement of Lewin's, drawing in particular on remarks made by Alec Jeffreys about the human globin cluster and Alu family, "that it is not a universal phenomenon."

Concerted evolution is occurring in the globin cluster; indeed this phenomenon was first defined as such in this cluster due to the homogenization of pairs of α and γ genes, and their flanking sequences, by unequal exchange or gene conversion. In reviewing such events in the globin cluster, Jeffreys has written, "clearly, concerted evolution is not a rare phenomenon, and seems to occur between even distantly related genes and between active genes and pseudogenes" (*2*). In the case of very large families, such as Alu, detailed consideration needs to be given to the rates of homogenization relative to the mutation rate. A 10 percent level of sequence variation between 10 cloned Alu repeats from the human genome (*3*) reflects the constraints on homogenization imposed by the presence of 500,000 copies finely dispersed over 46 chromosomes. Despite these constraints the very low levels of homology revealed by hybridization between human and mouse Alu families reflects a much greater divergence between species than within species. Furthermore, the human Alu family has been homogenized throughout by an imperfect dimer, while the mouse Alu family consists only of monomers (*3*). Turnover is occurring in the Alu family, albeit slowly. We are not aware of families, whether tandem or interspersed, genic or nongenic, that are immune from such processes. The evolutionary progress of each family under molecular drive and the subsequent interaction with natural selection are expected to be very different (*1*).

The importance of molecular drive as a genetic system can only be assessed by consideration of the way in which the genetic and phenotypic cohesion of a population is maintained. An instructive example is provided by the phenomenon of hybrid dysgenesis in *Drosophila*. In this example, the molecular process is one of transposition, one of the three mechanisms underlying molecular drive. A slow rate of transposition of P elements would lead to a genetic situation in which there would be little variation in the number of P's in each individual at any one time during the initial accumulation of the element. The small variance in P number would not lead to dysgenesis within the population, as is observed. A large difference, however, in P number between a P population and a non-P population does lead to dysgenesis. Precisely the same low variance pattern of fixation would result from the slow rates of unequal exchange or gene conversion involving the homogenization of existing families for one variant or another.

Given this cohesive system of genetics, which contrasts remarkably with the classical population genetics of single-copy genes, we allowed ourselves some freedom in speculating on its involvement in the origin of the ontogenetic and reproductive differences between species. So far as we are aware, there are few experimental tests of the genetic mechanisms that are thought to underlie species differences. We do not disagree with the conventional viewpoint that such differences might be consequential when natural selection and genetic drift are working within Mendelian populations. Nevertheless, such external processes of fixation are inadequate in explaining species differences in multiple-copy families, that is, the phenomenon of concerted evolution. The evolution of such families and their manifold phenotypic effects can be partly explained by the genetics of molecular drive, which is precisely based on internal molecular mechanisms of turnover. Consequently, we are perplexed that Ford Doolittle and Robert Selander consider our speculation on the evolutionary biology of molecular drive to be unhelpful. We consider that all evolutionary biology may be, in essence, a manifestation of molecular events, and the artificial separation of molecular and evolutionary biology is itself unhelpful.

Part of the problem seems to stem from a mistaken supposition that turnover is only observed in nongenic families whose biological effects have yet to be ascertained. Concerted evolution is an extensively documented observation in many multigene families. The biological effects and evolutionary significance of changes in these families cannot be seriously challenged. It could well be that even the species differences in behavior emphasized by John Maynard-Smith are under multigene control. A population could undergo a long-term collective transformation in behavior under the aegis of the genetic system of molecular drive.

We do not consider molecular drive to be a catch-all for all genomic rearrangements and exchanges. If some rearrangements, for example, inversions, deletions, or duplications, turn out to be one-off events, then they are analogous to most point mutations that rely for their evolutionary progress on selection and drift. They do not contribute to the process of molecular drive.

From what we now understand of the activities of unequal exchange, gene conversion, and transposition in so many different families, the evolutionary differences between species must be considered a complex outcome of three processes of fixation—adaptive, accidental, and cohesively driven. Despite the seeming pitfalls in trying to promote a new perspective, we see no reason to be unenthusiastic about the implications of molecular drive.

G. A. DOVER
T. STRACHAN
E. S. COEN
Department of Genetics, University of Cambridge, Cambridge CB2 3EH, England
S. D. M. BROWN
Department of Biochemistry, St. Mary's Hospital, London W2 1PG

References

1. G. A. Dover, S. D. M. Brown, E. S. Coen, J. Dallas, T. Strachan, M. Trick, in *Genome Evolution*, G. A. Dover and R. B. Flavell, Eds. (Academic Press, New York, 1982), pp. 343–372); G. A. Dover, *Nature (London)* **299**, 111 (1982).
2. A. Jeffreys, in *Genome Evolution*, G. A. Dover and R. B. Flavell, Eds. (Academic Press, New York, 1982), pp. 157–176.
3. W. R. Jelinek and C. W. Schmid, *Ann. Rev. Biochem.* **51**, 813 (1982).

Oncogenes

In his letter of 15 October (p. 214), John W. Littlefield points out that the cell line NIH 3T3 is an imperfect recipient for experiments designed to capture "oncogenes" by gene transfer from tumor cell genomic DNA. I agree. The